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Pancreas Resection and Islet Autotransplantation for End-Stage Chronic Pancreatitis

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Objective
To assess the safety and efficacy of islet autotransplantation (IAT) combined with total pancreatectomy (TP) to prevent diabetes.

Summary Background Data
There have been recent concerns regarding the safety of TP and IAT. This is thought to be related to the infusion of large volumes of unpurified pancreatic digest into the portal vein. Minimizing the volume of islet tissue by purifying the pancreatic digest has not been previously evaluated in terms of the postoperative rate of death and complications, pain relief, and insulin independence.

Method
During a 54-month period, 24 patients underwent pancreas resection with IAT. Islets were isolated using collagenase and a semiautomated method of pancreas digestion. Where possible, islets were purified on a density gradient and COBE processor. Islets were embolized into the portal vein, within the spleen and portal vein, or within the spleen alone. The total median volume of digest was 9.9 mL.

Results
The median number of islets transplanted was 140,419 international islet equivalents per kilogram. The median increase in portal pressure was 8 mmHg. Early complications included duodenal ischemia, a wedge splenic infarct, partial portal vein thrombosis, and splenic vein thrombosis. Intraabdominal adhesions were the main source of long-term problems. Eight patients developed transient insulin independence. Three patients were insulin-independent as of this writing. Patients had significantly decreased insulin requirements and glycosylated hemoglobin levels compared with patients undergoing TP alone. Of the patients alive and well as of this writing, four had failed to gain relief of their abdominal pain and were still opiate-dependent.

Conclusion
Combined TP and IAT can be a safe surgical procedure. Unfortunately, almost all patients were still insulin-dependent, but they had decreased daily insulin requirements and glycosylated hemoglobin levels compared with patients undergoing TP alone. A prospective randomized study is therefore needed to assess the long-term benefit of TP and IAT on diabetic complications.

Chronic pancreatitis is a progressive inflammatory disease causing irreversible structural damage to the pancreatic parenchyma. It culminates in permanent impairment of pancreatic exocrine function and, in severe cases, diabetes mellitus. The incidence has quadrupled in the past 30 years, and patient management remains a major challenge.[1] Patients generally have chronic, intractable abdominal pain that is often relieved only by large quantities of opiates, to which many patients develop tolerance and dependence. There is no agreement as to the best management strategy. Conservative approaches combine medical and supportive modalities (e.g., exocrine enzyme supplements, Octreotide®, and antioxidants), nerve blockade (e.g., celiac plexus block, thoracoscopic splanchnic nerve division), or partial resection when the disease is localized. Although these management strategies can be successful, most reports

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are anecdotal. They often show improvement only for patients with mild disease who are not opiate-dependent, and symptomatic relief is often transient. Other treatments for patients with ductal obstruction or ductal dilatation include ductal decompression, performed either surgically or endoscopically, but again symptomatic relief can be only transient.

Notwithstanding these treatment options, in a few patients conservative treatments fail and the quality of life becomes unacceptable. Total pancreatectomy (TP) can relieve pain, but it has remained unpopular because it renders the patient diabetic and is associated with high rates of postoperative death and complications. To date, the Minnesota group has the largest experience of TP and islet autotransplantation (IAT) (n = 48),[2] reporting that at least 74% of patients receiving more than 300,000 islets were still insulin-independent after 2 years of follow-up. In comparison, experience in Europe is limited.[3] The aim of this study was to assess prospectively the safety and efficacy of TP combined with IAT as a treatment strategy for end-stage chronic pancreatitis.

METHODS

Patients

Twenty-four patients (14 women, 10 men, median age 44 years) underwent pancreas resection and simultaneous IAT during a 54-month period (1994–1999). These patients were compared with 13 other patients (6 women, 7 men, median age 43 years) who underwent TP alone (controls) during the same period. In the latter group, IAT was attempted but failed in four patients as a result of extensive pancreatic calcification. All patients gave fully informed consent before pancreas resection. All patients were told that exogenous insulin would be needed for postoperative normoglycemia and that this would almost certainly be a life-long requirement. Permission was granted from the local ethical human subjects committee for the metabolic assessment and postoperative follow-up of these patients.

All patients were thoroughly evaluated by a consultant hepatobiliary surgeon (A.R.D.), consultant gastroenterologist, consultant pain specialist, clinical psychologist, and consultant endocrinologist. All patients underwent a 75-g oral glucose tolerance test (Nova Ltd., Leicester, UK) and a butterfat test (1 mg/kg) to assess pancreatic function. Based on World Health Organization criteria, all patients with normal and in some cases borderline results on glucose tolerance tests[4] underwent IAT. Other investigations included endoscopic retrograde cholangiopancreatography, diagnostic laparoscopy, abdominal computed tomography, abdominal ultrasound, and in one patient abdominal magnetic resonance imaging. In all but one patient, the indication for surgery was intractable abdominal pain of 1 to 15 years' duration. The other patient required surgery because of an extensive pseudocyst with compression symptoms.

For the patients undergoing IAT, the causes of pancreatitis are summarized in Table 1. In two patients, pancreatitis seemed to develop after a mild episode of abdominal trauma with no other apparent explanation. All but one patient required analgesia with opiates for symptomatic relief of pain. Overall, 50% of the IAT patients had undergone previous therapeutic procedures for pain relief, but in most the benefit was transient. These included celiac plexus or thoracoscopic nerve ablation (n = 4), distal pancreatectomy (n = 3), sphincterotomy (n = 4), drainage procedure (n = 6), or cystgastrostomy (n = 2). No patient had previously undergone a longitudinal pancreaticojejunostomy. This procedure disrupts the integrity of the pancreatic duct; if the patient needed a further procedure because of inadequate pain relief, future IAT would be problematic because of the need to administer collagenase into the duct.

Total Pancreatectomy

Pancreatic resections were defined as a TP if all the gland was removed (n = 19). The procedure was considered a subtotal pancreatectomy if the pancreas was divided across the portal vein and the pancreatic head remained in situ (n = 2). In completion TP, the patient had previously undergone a distal pancreatectomy (n = 3). In the IAT patients, a pylorus-preserving procedure was performed (n = 16) or initially a duodenal-preserving procedure (n = 4). In the TP-alone group, the whole pancreas was excised as a one-stage procedure (n = 13).

Islet Transplantation

After pancreas excision, pancreatic islets were isolated using intraductal collagenase and a modified automated method,[5] as previously described.[6] Islets were isolated using collagenase P (Boehringer Mannheim, Germany) in the first 20 patients and a purified enzyme blend thereafter (Human Liberase, Boehringer Mannheim). In 15 patients, islets were purified on a continuous density gradient (Ficoll-amidotrioazoate–based) layered onto a COBE 2991 processor (COBE, Lakewood, CA), as described elsewhere.[7] Islet purity was determined subjectively by a visual assessment using two 100-μL sampling strips. A comparison was made comparing the relative quantity of dithizone-stained islets (red) to unstained acinar tissue (yellow).[7] To minimize the infused volume of pancreatic tissue, only volumes of digest in excess of 14 mL were purified. This was deemed an acceptable limit based on previous reports describing significant postoperative complications secondary to intraportal infusion of islet autografts[2,8–12] and allografts.[13] Islet yields were expressed as international islet equivalents (IEQ) (islets 150 μm in diameter).[14,15]

Islets were prepared while the surgeons completed the enteroenterostomy and choledochojejunostomy reconstruction. Approximately 2 hours after pancreas excision, the islets were returned to the operating room. Intraportal infu-

Table 1. SUMMARY OF RESULTS

Age/ Sex	Cause	Symptoms (months)	Preop. Pethidine (per 24h)*	Postop. Petridine (per 24h)*	Resection	Islet Number (IEQ/ kg)	Insulin Independence (days)
52 M	Alcohol	48	400 mg	None	Total	6,757	9 (254–263)
52 F	Idiopathic	24	600 mg	40 mg	Total	9,240	1,098 (147–1,245)
43 M	Idiopathic	60	500 mg/SD 150 mg	None	Completion	1,640	–
45 F	Biliary pancreatitis	36	200 mg/SD 100 mg	None	Total	4,340	7 (244–251)
21 F	Alcohol	24	700 mg	350 mg	Total	5,027	–
46 F	Idiopathic	144	400 mg	None	Total	4,230	–
60 M	Alcohol	36	600 mg	–	Total	2,000	Died
52 F	Alcohol/hypercalcemia	60	SD 150 mg		Total	815	367 (41–409)
49 M	Alcohol	36	100 mg	None	Subtotal	320	1095† (7–1,113)
49 F	Idiopathic/trauma	18	200 mg	None	Total	882	–
31 F	Idiopathic	36	200 mg Ibu 3,200 mg	40 mg	Total	405	–
35 F	Idiopathic	60	200 mg	None	Total	1,585	
33 F	Alcohol	24	2,100 mg	–	Total	6,640	41 (162–203) Died 6 months
24 F	Idiopathic	14	1,000 mg	None	Total	509	–
48 F	Idiopathic	12	200 mg/SD100 mg	None	Total	1,575	54 (181–235)
61 F	Billiary pancreatitis	48	450 mg	200 mg	Total	2,874	35 (365–400)
36 M	Alcohol	100	400 mg	–	Total	2,314	Died 2 yr
33 F	Idiopathic	20	200 mg/SD150 mg	None	Total	1,250	–
60 M	Idiopathic	12	400 mg	None	Subtotal	1,546	579† (9–601)
48 F	Idiopathic/trauma	120	400 mg	None	Completion	1,060	–
27 F	Idiopathic	24	200 mg/SD150 mg	400 mg	Total	2,020	–
28 M	Divisum	48	100 mg	None	Total	2,512	–
39 M	Idiopathic	18	500 mg	None	Completion	610	
38 M	Alcohol	100	100 mg	None	Total	2,359	60† (47–107)

SD, sodium diclofenac (Voltarol®; Ibu, ibuprofen.)
* Equianalgesic does pethidine equivalent.
† Currently insulin-independent.

sion was performed using an 11-gauge silicon catheter (Vygon, Ecouen, France) placed in an omental vein and advanced into the left branch of the portal vein. Splenic islet infusion (n = 5) was performed by retrograde venous reflux, as described elsewhere.[16] All patients received 5,000 IU intravenous heparin before islet infusion. Islets were slowly infused for a period of 30 minutes.

Portal venous pressure, mean arterial pressure, and central venous pressure were measured intermittently during islet infusion. All invasive pressures were measured using electronic transducers connected to an anesthetic monitor (General Electric, Marquette System, UK). The transducers (DPT 6003 pressure transducer, Avon Medicals, Kent, UK) were zeroed to atmospheric pressure and placed at the level of the right atrium. Arterial pressure was measured using a 20-gauge catheter (Arrow International, PA) positioned in the radial artery at the induction of anesthesia. Central venous pressure was measured using an 18-gauge polyurethane triple-lumen right internal jugular venous catheter (Vygon). Both pre- and postislet infusion pressures were compared so that the volume effects of the islet infusion could be taken into consideration. Portal venous pressure was measured with a catheter placed in the left portal vein. At the end of islet infusion, the portal catheter and portal venous system were flushed with 200 mL of 0.9% normal saline (Baxter Healthcare, Thetford, UK).

Postoperative Care

All patients received high-dependency or intensive care for at least 24 hours with epidural anesthesia (fentanyl and 0.5% bupivacaine). Blood glucose was initially controlled at 3 to 7 mmol using an intravenous insulin (Actrapid, NovoNordisk, UK) sliding scale in conjunction with 8 IU subcutaneous insulin (Humulin I; Lilly, Basingstoke, UK) administered twice daily.

Assessment of Graft Function

Islet graft function was assessed by C-peptide radioimmunoassay (CIS Bio International, Nivelles, Belgium) at 1, 3, 6, and 12 months. Patients were asked to omit exogenous insulin for at least 12 hours beforehand, in addition to an overnight fast before blood sampling the morning after. A functioning graft was defined as a C-peptide level of more than 0.5 ng/mL, and not as insulin independence, as recently

recommended by the International Pancreas and Islet Transplant Association.[17] Glycosylated hemoglobin (HbA1c) levels were measured throughout the 5 years of follow-up by high-performance liquid chromatography on a Mono S column (Pharmacia, Milton Keynes, UK). Results of insulin requirements and HbA1c were compared between patients undergoing IAT (n = 24) and those undergoing TP alone (n = 13). An evaluation of insulin independence was also made in relation to patients receiving more than 2,500 IEQ/kg. This has recently been recommended to be the critical islet mass to achieve insulin independence in IAT recipients.[18]

Statistical Analysis

Results are expressed as median (range) values and expressed graphically as 95% confidence intervals where appropriate. Temporal differences between C-peptide measurements were compared using the Kruskall-Wallis one-way analysis of variance test. Continuous variables were analyzed by the nonparametric Mann-Whitney test. Differences between 24-hour insulin requirements at different time points were also compared by the nonparametric Mann-Whitney test. Categorical data were examined by the Fisher exact test. Statistical significance was taken to be $P < .05$.

RESULTS

All results, unless otherwise stated, will apply to patients undergoing IAT. In the IAT cohort, 22 patients had normal glucose tolerance before surgery. Three patients had previously undergone a distal pancreatectomy. Two of these patients had borderline and one abnormal results on glucose tolerance testing. Two patients had a family history of diabetes (non-insulin-dependent, n = 1; insulin-dependent, n = 1). All patients had abnormal results on butterfat tests. Analgesic requirements are summarized in Table 1 and have been converted to equianalgesic pethidine equivalents where possible. The median body mass index was 22.7 kg/m^2 in men and 18.9 kg/m^2 in women.

As previously described, TP was the most common procedure in patients undergoing IAT (n = 18). The spleen was preserved in 19 patients (80%). The median duration of the procedure was 470 minutes (range 370–620) and median blood loss was 970 mL (range 200–4,000).

The median pancreas weight was 71 g (range 31.8–127). The median number of islets (IEQ) isolated per gram of pancreas was 1,531 (range 249–5,027). Purifying the pancreatic digest did not significantly reduce the yield of islets obtained. The total median number of islets received by patients having a purified graft (n = 15) was 127,964 IEQ versus 44,116 IEQ for those receiving a unpurified graft (n = 9) ($P > .05$). This was unexpected, given that islet purification can reduce islet yields. The reason for this discrepancy is that the prepurified pancreatic digest in the recipients having a purified graft autograft was initially a larger volume (>14 mL). The addition of purification optimized islet yield into a smaller volume by separating islet tissue from acinar tissue. In contrast, the pancreatic digest was not purified in the remaining patients because the volume was already too small to be purified (<14 mL), and it consequently contained fewer islets. The overall median volume of islet tissue infused was 9.9 mL (range 3–14). The sites used for transplantation are summarized in Table 2.

Table 2. TRANSPLANT SITES

Site	Intraportal (n = 19)	Spleen (n = 2)	Combined (n = 3)
Volume of islet Tissue (mL) (IEQ/kg patient)	9.0 1,820	6.5 849	14.0 5,027
Change in portal presure (mmHg)	4.0	12.0	13.5
Transient insulin independence (%)	8 (44)*	1 (50)	1 (33)

All median values.
* IEQ, international islet equivalents (150 μm).
* Three patients are currently insulin-independent (two subtotal resections).

Complications related to the islet autotransplant infusion occurred in three patients. One patient who received a purified, combined intraportal and splenic islet graft (13.5 mL) developed a partial portal vein thrombosis after the first postoperative week; it required systemic anticoagulation with warfarin for 6 months. Two other patients developed complications related to splenic islet infusions (wedge splenic infarction, n = 1; thrombosis of splenic venous outflow requiring a splenectomy, n = 1); these have been described elsewhere.[16] Portal pressure transiently increased by 8 mmHg (range 0–16). In the first 12 postoperative months, all patients underwent splenic ultrasound and power Doppler assessment of splenic vascularity. After surgery, no other vascular abnormalities were detected.

The overall 30-day death rate in all 37 patients was 5.5% (IAT group, n = 1; TP-alone group, n = 1). The patient in the IAT group was one of the oldest in the series (60 years) and died of a cerebrovascular accident 4 weeks after surgery. At the post mortem, he was found to have a carotid stenosis. The other patient (69 years) had chronic renal allograft nephropathy and was immunosuppressed.

Complications related to the pancreatectomy in IAT patients are summarized in Table 3. Duodenal-preserving pancreatectomy was attempted in the first four patients, with three eventually needing duodenal resection because of ischemia. This technique has since been abandoned in favor of pylorus-preserving pancreatectomy. Only nine patients had immediate postoperative complications (38%); five were relatively minor complications. Adhesions (n = 6) were the most common cause of late postoperative problems

Table 3. DEATHS AND COMPLICATIONS

Immediate (n = 9)	Late (n = 8)	Further Surgery (n = 11)
Chest infection/pleural effusion (n = 2)	Intraabdominal adhesions (n = 6)	Laparotomy or laparoscopic division of adhesions (n = 6) (Jones tube insertion n = 2)
Septicemia (n = 1)	Duodenal ischemia (n = 2)	Drain site abscess (n = 1)
Wedge splenic infarct (n = 1)*		Splenectomy (n = 1)
Duodenal ischemia (n = 1)		Duodenal resection (n = 3)
Cerebrovascular accident		
Intraabdominal abscess/collection (n = 1)		
Partial portal vein thrombosis (n = 1)*		
Splenic thrombosis (n = 1)*		
Drain site abscess (n = 1)		

* Related to islet autotransplant.

in 25%. Symptomatic adhesions recurred in two patients but were less troublesome after insertion of a Jones tube for 6 weeks. There were two late deaths, both in alcohol-dependent patients (6 months and 2 years) and both unrelated to surgery.

One late death occurred in the TP-alone group; this patient also continued to have a heavy alcohol intake. Immediate surgical complications in the TP-alone group occurred in four patients (30%): splenic abscess (n = 1) drained percutaneously, biliary leak requiring revision of a choledochoenterostomy (n = 1), and respiratory tract infection (n = 2). As in the IAT group, adhesions and intermittent small bowel obstruction caused late problems in three patients, who required further surgery. One further patient developed a gastrocolic fistula 14 months after surgery.

The median hospital stay was 24 days (range 10–64) in the IAT group and 17 days (range 7–66) in the TP-alone group. Follow-up as of this writing was 15 months to 5 years. Of the 21 patients in the IAT group who were alive and well, 16 (77%) no longer required regular analgesia; only 5 (23%) still required opiates. In comparison, of the 11 patients alive and well in the TP-alone group, 7 (63%) no longer required regular analgesia and 4 were still opiate-dependent.

All patients had functioning islet autografts (Fig. 1) and 11 (45%) had developed periods of insulin independence (range 7 days to 3 years), but only 3 patients were insulin-independent as of this writing. Two of these patients underwent subtotal pancreas resections. Of the 9 patients receiving approximately 2,500 IEQ/kg, 7 developed insulin independence (77%); of the 14 who received less than 2500 IEQ/kg, 5 developed insulin independence (35%; $P = .31$). During the study period, IAT recipients had significantly lower HbA1c levels (median 6.7% vs. 8.5%; $P = .007$; Fig. 2) and 24-hour insulin requirements (Fig. 3, Table 4) compared with patients receiving TP alone.

DISCUSSION

There is no agreement as to the best management plan for patients with chronic pancreatitis. Most of these issues have been discussed elsewhere.[1,2,19–21] Nonetheless, most investigators believe that TP is not a popular choice for patients with end-stage chronic pancreatitis because it is associated with appreciable rates of complications (50%) and death (6%).[17,22–28] After TP, up to a third of patients do not obtain adequate pain relief and will still require opiate-derived analgesia.[19] All patients become diabetic, with very labile diabetes; for patients who continue to have heavy alcohol ingestion, this may culminate in late death (40%).[1,19] The rationale for the combined TP and IAT procedure is that if diabetes could be avoided by simultaneous IAT, TP would be a more acceptable treatment, on the proviso that good rates of pain relief can be achieved. The current study was designed to study prospectively the validity, safety, and efficacy of TP combined with IAT. Perioperative rates of death and complications, pain relief, insulin independence, and diabetic control were considered as specific end points.

Experience of simultaneous IAT and TP has largely been

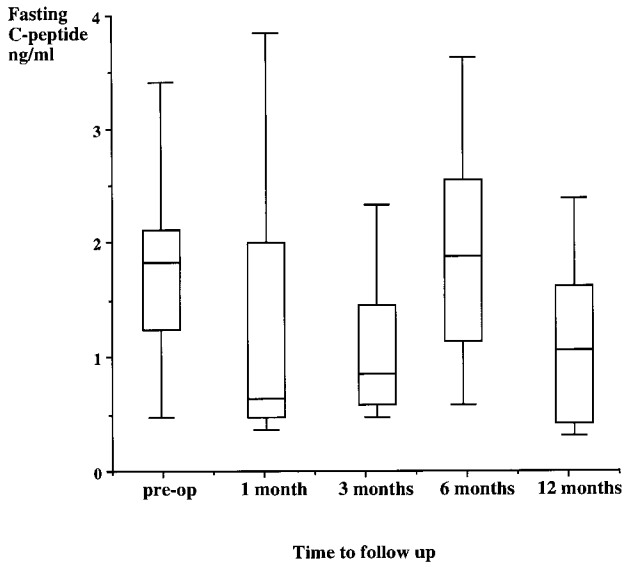

Figure 1. Temporal secretion of basal C-peptide after islet cell autotransplantation. Box plots represent median, 95% confidence intervals, and range values. Kruskall-Wallis one-way analysis of variance test, $P > .05$.

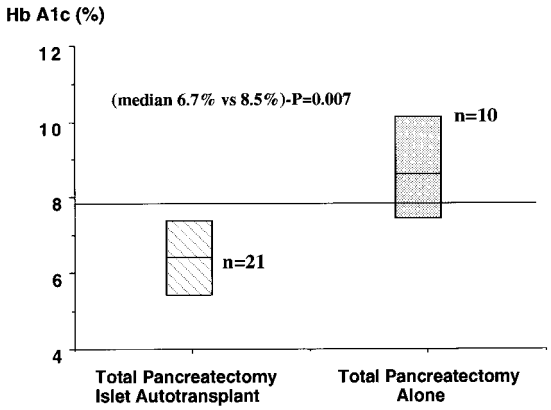

Figure 2. Comparison of hemoglobin A1c (%) levels. Box plots represent median and 95% confidence intervals (Mann-Whitney test, $P = .007$). During follow-up (15 months to 5 years), the mean hemoglobin A1c level was calculated for each patient, and the mean value is plotted for islet autotransplant recipients (n = 21) and patients undergoing total pancreatectomy alone (n = 10).

described in the United States by the Minnesota group.[2] However, concerns remain regarding the safety of islet infusion. Large volumes of unpurified pancreatic digest infused into the portal vein or spleen have led to worrying reports of portal hypertension,[2,8,9,29,30] hepatic infarction,[10,11] disseminated intravascular coagulation,[8] splenic hemorrhage,[2] and death.[10,11] Most of these complications are thought to be related to the release of high levels of tissue thromboplastin (tissue factor) in the islet graft, in addition to activation of the trypsin cascade.[12,31,32] We therefore attempted to minimize the final infused volume of pancreatic tissue by purifying all pancreatic digest exceeding 14 mL in volume. We hoped that this strategy would lead to minimal complications, with no deaths and insulin independence. In this series, 15 of 24 patients received purified islet autografts and 9 patients received unpurified autografts.

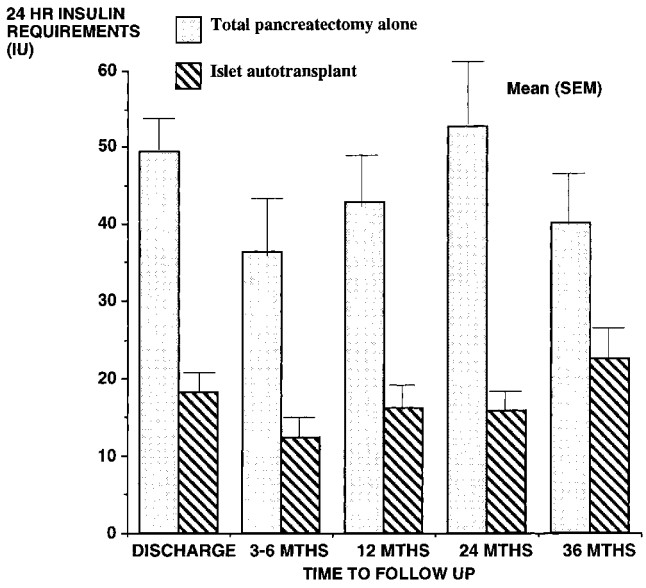

Figure 3. Comparison of 24-hour insulin requirements (IU/24 hours) in islet autotransplant recipients and those undergoing total pancreatectomy alone. Plots represent mean values and standard error.

Table 4. INSULIN REQUIREMENTS AT FOLLOW-UP

	Discharge	3–6 mo	12 mo	24 mo	36 mo
IAT	18.2 (12.7–23.7)	12.3 (6.6–18.0)	16.1 (9.3–22.9)	15.8 (9.7–21.9)	22.6 (10.9–34.2)
TP alone	49.3 (37.9–60.7)	36.3 (13.6–60.0)	42.8 (32.0–53.7)	52.5 (17.2–87.0)	40.0 (10.2–69.8)
P value*	.002	.002	0019	.005	

IAT, islet autotransplant; TP, total pancreatectomy.
Data are given as mean IU per 24 hours (95% confidence interval).
* Mann=Whitney test.

Despite islet purification, there were three complications related to islet infusion (see Table 3): partial portal vein thrombosis, splenic vein thrombosis (requiring a splenectomy), and a wedge splenic infarct. All these patients received an islet infusion into the spleen; in two of these, the islet autografts were unpurified. For several reasons, the spleen has since been abandoned, as previously discussed.[33] Briefly, these reasons include the difficulty in preventing reflux of islets into the portal vein,[16] the variability of portosystemic anastomoses that can result in islet pulmonary emboli,[12] and splenic preservation on the short gastric veins after pancreas resection.[33] More importantly, none of the complications in this series were fatal, as has been historically documented by other investigators.[10,11] In the reported series, the largest volume of islet tissue administered was 14 mL, compared with 35 mL in the Minnesota series.[2] The latter group also reported greater portal pressures after islet infusion (mean 23.9 cm H_2O vs. 11.5).[2] The surgeons in the Minnesota group prefer to transplant unpurified pancreatic digest on the premise of optimizing islet mass, but perhaps at the expense of increased portal pressures and associated complications. Our results suggest that islet purification can reduce the volume of pancreatic digest, making an intraportal transplant a potentially safer procedure but at the expense of compromising islet mass and insulin independence.

Perioperative rates of death and complications related to the pancreas resection compared favorably with those of other large series.[19,22–28] However, duodenal ischemia was an initial problem in three of the first four patients. This has since been overcome by using a pylorus-preserving technique of pancreas resection. In the long term, adhesions were the most common cause of problems; this may have been related to the duration of the surgical procedure and the general chronic inflammatory process that is a well-recognized feature of chronic pancreatitis. We hope that

with future developments in adhesion-prevention barriers, such as bioresorbable membranes, this complication may be overcome.[34]

In the most recent International Islet Transplant Registry Report (1990–1998), 114 well-documented cases of TP and IAT are described. At least 50% of these patients remained insulin-independent at 1 year; 69% were insulin-independent for more than 7 days.[35] The Minnesota group showed that 34% of patients having total or near-total (>95% resection) pancreatectomy remained insulin-independent for 2 to 10 years. More importantly, no grafts had failed after 2 years. These observations compare but do not completely agree with those reported here. In our experience, it has been difficult to prevent diabetes consistently and permanently, in the presence of acceptable rates of pain relief, complications, and death. However, lower daily insulin requirements and HbA1c levels can be achieved. Long-term follow-up studies are therefore required to determine whether these observations can be maintained, with the potential of reducing the risks of developing diabetic complications and improving quality of life.

Several explanations can account for some of the reported differences in rates of insulin independence. The Minnesota series documented 16 patients undergoing a near-total resection (>95%).[2] It is impossible to estimate what proportion of islet mass remained in situ after partial pancreas resection and to what extent this contributes to overall insulin secretion in vivo. In our series, all but two patients underwent complete resection, and insulin independence was achieved indefinitely only in these patients. Moreover, Fontana et al[35] described 24 patients who underwent partial resection combined with IAT: 23 of them developed long-term insulin independence. These data therefore suggest that the residual pancreas is a critical determinant for achieving insulin independence.

Recent reports have indicated that at least 2,500 IEQ/kg is crucial for insulin independence.[18] Of the patients receiving approximately 2,500 IEQ/kg in this series, 77% developed transient insulin independence, compared with only 35% of those receiving less than 2,500 IEQ/kg. In the Minnesota experience, the mean number of islets transplanted per patient was 345,500,[2] compared with 140,419 in our series. Given that better rates of insulin independence were achieved by the Minnesota group, the lower number of islets transplanted in this study was probably insufficient to achieve long-term insulin independence.

Although the functional islet mass is an important determinant for achieving insulin independence, the overall outcome is likely to be multifactorial. The poor islet yields in this series may be related to the pathogenic severity of the pancreas before processing. Overall, at least a third of the patients were known to be alcohol-dependent, compared with 18% in the Minnesota series,[2] and in our experience, islet isolation in this cohort of patients is often difficult because of extensive pancreatic calcification and fibrosis. We have also found that it is sometimes impossible to purify severely damaged pancreatic tissue to an adequate degree. This may be related to the similar tissue densities of islets and acinar tissue in a chronically inflamed pancreas, but this has not been specifically investigated.

More recently, it has been suggested that completely purified islets may trigger apoptosis,[36] and islets with a rim of acinar tissue (mantle islets) may in fact be more suitable for transplantation.[37] This is because exocrine tissue exerts trophic influence on beta cells,[38] and precursor cells in the ductal epithelium may trigger proliferation and differentiation (nesidioblastosis).[39] Studies have also shown that some of the reagents used for islet purification may be toxic to islets because of high levels of contaminating endotoxins.[40] Nevertheless, endotoxin appears to be most abundant in the collagenase, but not in Human Liberase,[41] which is now preferred by all centers performing clinical islet transplantation.

The intraportal site has long been considered a suboptimal site for islet transplantation. Increasing evidence shows that it may not provide physiologic regulation of glucose[42] or insulin secretion.[43] Studies in humans have also demonstrated failure of intrahepatic islets to respond to insulin-induced hypoglycemia by glucagon secretion.[44] Other peculiarities of the intraportal site are that newly implanted islets are bathed in high levels of gastrointestinal-derived endotoxins.[45] The liver is also an important part of the reticuloendothelial system, with a large population of macrophages that produce many toxic metabolites, including oxygen free radicals, nitric oxide, and other potent cytokines that may be detrimental to islet engraftment.[46,47] With the mixture of both portal venous and hepatic artery blood, oxygen tensions may be inadequate to support organelles with such a high metabolic demand. Indeed, studies in rodents suggest that islets transplanted in the renal subcapsular space, even 1 month after transplantation, have oxygen tensions at least 50% of that in the native pancreas.[48]

Although some of these mechanisms can explain why some islet autografts fail to achieve insulin independence, it is difficult to explain the gradual deterioration in C-peptide levels between 6 months and 1 year. In IAT patients, C-peptide levels deteriorate much earlier in the postoperative course. Many factors can explain this, but both alloreactivity and autoimmunity are the most important.[49] This finding was recently highlighted by the surgeons in the Miami group, who suggested that islet allografts are subject to a process of chronic rejection that can be slowed by supplementing a partially functioning islet allograft with small doses of exogenous insulin.[50] This effect is probably mediated by exogenous insulin slowing the process of islet exhaustion. This could also apply to islet autografts: we have observed that some patients can achieve near-normoglycemia, without rapid deterioration of C-peptide, when small doses of exogenous insulin (e.g., 2–10 units/24 hours) are administered. In short, some IAT patients show a gradual deterioration in C-peptide levels that is not completely understood but may be related to islet exhaustion and chronic overstimulation in recipients with a marginal islet

mass. In support of this, two studies[43,51] have documented that IAT patients have higher serum concentrations of proinsulin, suggesting that beta cells are secreting immature insulin granules. Another explanation could be portosystemic overspill of islet hormones, because the islets are located in the end-portal venous sinusoids.[43] In theory, the addition of small doses of exogenous insulin could slow the process of islet exhaustion in the absence of any islet alloimmunity and islet autoimmunity.

Taking into account some of these factors, the results of IAT are likely to improve as investigators have an increased understanding of islet isolation[45] and islet vulnerability in the early postoperative period.[52] Some of these advances include using newer endotoxin-free reagents[40,41] combined with better cold storage methods.[53,54] Treatments to reduce the inflammatory response after islet embolization that were not used in this study may include antioxidants,[55] nicotinamide,[56] and new chimeric cytokine antagonists (e.g., infliximab). Nevertheless, experimental evidence supporting the use of these agents remains anecdotal.

In conclusion, there is still no ideal surgical procedure for patients with end-stage chronic pancreatitis. Pancreatectomy combined with IAT can be a safe procedure, producing acceptable rates of complications and pain relief with a low death rate. Unfortunately, almost all patients remain insulin-dependent, and the reasons for this are likely to be multifactorial. Nevertheless, these patients have lower daily insulin requirements and significantly better glycemic control, based on HbA1c levels. Whether the effect of good pain relief at the expense of diabetes will improve the patient's quality of life compared with the lower rate of pain relief with insulin independence offered by a subtotal resectional procedure remains to be proven. A prospective, randomized controlled trial is required to study the long-term benefits of TP and IAT.

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